Cost-effectiveness of internet-based training for primary care clinicians on antibiotic prescribing for acute respiratory-tract infections in Europe

Oppong, Raymond; Jowett, Sue; Roberts, Tracy

DOI:
10.1093/jac/dky309

Cost-effectiveness of internet-based training for primary care clinicians on antibiotic prescribing for acute respiratory-tract infections in Europe

Raymond OPPONG[1], Richard D SMITH[2], Paul LITTLE[3], Theo VERHEIJ[4], Christopher C BUTLER[5], Herman GOOSSENS[6], Samuel COENEN[6,7], Sue JOWETT[1], Tracy E ROBERTS[1], Felix ACHANA[8], Beth STUART[3], Joanna COAST[9*]

[1]*Health Economics Unit, Institute of Applied Health Research, Public Health Building, University of Birmingham, Birmingham, United Kingdom, B15 2TT*

[2]*Faculty of Public Health and Policy, 15-17 Tavistock Place, London School of Hygiene and Tropical Medicine, London, United Kingdom, WC1H 9SH*

[3]*Primary Care and Population Sciences Division, Aldermoor Health Centre, Aldermoor Close, University of Southampton, Southampton, United Kingdom, SO16 5ST*

[4]*Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, Netherlands*

[5]*Nuffield Department of Primary Care Health Sciences, University of Oxford, New Radcliffe House, Radcliffe Observatory Quarter, Woodstock Road, Oxford, United Kingdom, OX2 6NW*

[6] *Laboratory of Medical Microbiology, Vaccine & Infectious Disease Institute (VAXINFECTIO), University of Antwerp, Antwerp Belgium*

[7]*Centre for General Practice, Department of Primary and Interdisciplinary Care (ELIZA) Vaccine & Infectious Disease Institute, University of Antwerp, Antwerp Belgium*

[8] *Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, United Kingdom CV4 7AL*

9 Health Economics at Bristol, Health and Population Sciences, Bristol Medical School , University of Bristol, Bristol United Kingdom, BS8 2PS

Address for correspondence:

Joanna Coast, Health Economics at Bristol, Health and Population Sciences, Bristol Medical School, University of Bristol, Bristol United Kingdom, BS8 2PS Email: jo.coast@bristol.ac.uk

Running title: Cost-effectiveness of internet-based training on antibiotics prescribing

Abstract

Objectives: Overprescribing of antibiotics by general practitioners is seen as a major driver of antibiotic resistance. Training in communication skills and C-reactive protein (CRP) testing both appear effective in reducing such prescribing. This study assesses the cost-effectiveness of (i) training general practitioners (GPs) in the use of CRP testing, (ii) training GPs in communication skills and (iii) training GPs in *both* CRP testing and communication skills compared to usual care.

Methods: Economic analyses (cost-utility analysis (CUA) accounting for the cost of antibiotic resistance and cost-effectiveness analysis (CEA)) were both conducted from a health care perspective with a time horizon of 28 days alongside a multinational, cluster, randomised, factorial controlled trial in patients with respiratory tract infections in five European countries. The primary outcome measures were QALYs and percentage reductions in antibiotic prescribing. Hierarchical modelling was used to estimate an incremental cost-per-QALY-gained and an incremental cost-per-percentage-reduction in antibiotic prescribing.

Results: Overall, the results of both the CUA and CEA showed that training in communication skills is the most cost-effective. However, excluding the cost of antibiotic resistance in the CUA resulted in usual care being the most cost-effective option. Country-specific results from the CUA showed that training in communication skills was cost-effective in Belgium, UK and Netherlands whilst training in CRP was cost-effective in Poland.

Conclusion: Internet-based training in communication skills is a cost-effective intervention to reduce antibiotic prescribing for respiratory tract infections in primary care if the cost of antibiotic resistance is accounted for.

Introduction

Antibiotic resistance is currently one of the world's leading public health concerns, which places a heavy burden on scarce resources. In the UK, resistant infections such as MRSA are estimated to cost the National Health Service an additional £1 billion in extra treatments annually[1] and without a resolution 'superbugs' are estimated to cause more deaths than cancer by 2050, costing about $100 trillion globally.[2]

The difficulty in determining who will benefit from prescribing, and desire to satisfy patients demands, appear to be driving inappropriate and over-prescribing of antibiotics by general practitioners (GPs).[3-5] As well as impacting upon the development of resistance, antibiotic prescribing is associated with significant costs.[6] The National Health Service in the UK incurs an annual cost of between $35(£23) and $70(£47) million in antibiotic prescription costs for acute cough/lower respiratory tract infections alone for example.[7] Reducing the inappropriate and over-prescribing of antibiotics would thus not only help reduce the problem of antibiotic resistance but also save scarce resources.

The rate of development of new antibiotics has slowed down over the past three decades[8-11] and the antibiotics currently available must be conserved. One way to assist with this protection is to find cost-effective ways of changing prescribing behaviour of GPs.

Interventions to reduce prescribing, based on persuasion, have generally been ineffective in dealing with the problem[12-13], and so more recent focus has turned to training GPs in advanced consulting skills and using point of care tests. These have resulted in a change in their prescribing behaviour,[14,15] with internet-based training programmes providing a reduction in antibiotic prescribing similar to the standardized methods of training.[16] Such internet-based training was developed by the Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe (GRACE) consortium.[4,17-18] The interventions consisted of (i) training GPs in the use of C-reactive protein testing (‘CRP’), (ii) training GPs in communication skills (‘communication skills’) and (iii) training GPs in *both* CRP testing and communication skills (‘combined’).

Results from the GRACE INTRO trial indicates that all three of these interventions (i) CRP (ii) communication skills and (iii) combined are effective in changing GP antibiotic prescribing behaviour.[19] However, in addition to the effectiveness of these interventions, it is important to determine whether the interventions provide value for money. One study conducted a cost-effectiveness analysis using reductions in antibiotic prescribing as an outcome measure and found all three interventions to be cost-effective compared with usual care.[20] However, no study has assessed the cost-effectiveness of these interventions in a multinational setting or estimated the country-specific cost-effectiveness of these interventions. The aim of this study is to assess the cost-effectiveness of these interventions across five European countries.

Patients and methods

Patients and settings

The economic analysis was conducted alongside a multinational, cluster, randomised, factorial controlled trial in which participating practices were randomised to one of four study groups (i) CRP, (ii) communication skills, (iii) combined and (iv) usual care.[19] The perspective adopted was that of the health service, including costs to the health service and health care cost to the patient. Consenting participants who presented with respiratory tract infections were recruited from primary care networks across five countries in Europe: Belgium, Netherlands, Poland, Spain, and the United Kingdom (England and Wales). The study was approved by ethics committees in all countries and all eligible individuals provided written consent before participating in the study. Full details of the clinical trial and intervention have been published elsewhere.[4,17-19]

Data collection

Resource use

The main sources of resource use information were the case report form (CRF) completed by primary care clinicians at the day of the consultation (day 1), and a diary completed by patients over a four-week period starting at day 1. Resource use data were collected on the following: consultations with health professionals, use of medications (over-the-counter and on prescription), medical investigations and hospital admissions.

Unit costs

Unit costs specific to each participating country were obtained mainly from national and international sources. In cases where costs were not available, they were obtained from a study previously published by the authors.[21] These costs were inflated to 2016 prices using the consumer price index for each country.[22] Where unit costs were unavailable, a market basket approach[23] was used to estimate a relationship between the UK and the country of interest to obtain this cost. The UK was chosen because all unit costs were available for this setting.

Medications were classified into 13 different groups. As it was not feasible to obtain unit costs for each individual drug for each country, a cost was generated for each of the 13 groups by estimating an average price from a list of drugs within that group. Table 1 gives a summary of the various sources of unit costs.

Intervention costs

For CRP, capital costs were obtained from the manufacturer (Orion Diagnostica) who quoted an average cost of €1,200. This cost was then annuitized assuming that the machine has a lifespan of three years, at an interest rate of 3.5%, and a cost-per-patient estimated. The costs of the reagents used (€7.45 (£6) per patient) were obtained from the provider (Oxford Biosystems).

With respect to the communication skills, the cost of the booklet given to patients, €0.36 (£0.29), was obtained from study coordinators and converted to country equivalent costs using the market basket approach.[23] For the combined intervention, the cost of the CRP machine and the cost of booklet estimated above were included.

To estimate the cost of the internet-based training, we obtained information on the amount of time GPs spent on it in each arm and estimated the total cost of time spent on training. This value was divided by the number of patients per GP to estimate the cost per patient. GPs spent on average 26.54 minutes, 37.44 minutes and 39.76 minutes on training in the CRP, communication skills and combined intervention arms respectively. Information on training has been published in a previous study.[4] GPs also received face-to-face training in using the CRP device and a similar approach to that described above was used to estimate a cost per patient in each arm. All costs were converted to Euros using purchasing power parities. In addition to presenting costs in Euros, costs were also presented in Pounds Sterling. All costs are presented in 2016 prices.

Previous research has highlighted the importance of including the cost of antibiotic resistance in economic evaluations assessing interventions in this area.[24-25] As a result of this, cost of resistance figures generated from a recent study[25] were added to every antibiotic prescription irrespective of the trial arm. The inclusion of these costs was limited to the cost-utility analysis since the outcome for the cost-effectiveness analysis (percentage reduction in antibiotic prescribing) indirectly accounts for antibiotic resistance given the fact that antibiotic prescribing leads to antibiotic resistance.

Health outcomes

Health outcomes were measured using the three-level version of the EQ-5D questionnaire. This instrument comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with three levels: no problems, some problems and severe problems.[26] Patients were asked to complete the EQ-5D-3L questionnaire over the entire four week period (at day 1, and at the end of weeks 1, 2, 3 and 4), or until they felt better. EQ-5D-3L index scores were generated using the European Harmonised Tariff [27] and have been validated for use in respiratory disease.[28]

Antibiotic prescribing

Physicians were asked to state whether they prescribed an antibiotic and this information was used to estimate the rate of antibiotic prescribing in each of the trial arms.

Statistical analysis

The economic evaluation comprised two main analyses: a cost-utility analysis (CUA; cost per QALY gained) and a cost-effectiveness analysis (CEA; cost per percentage reduction in antibiotic prescribing). Both were carried out on an intention to treat basis. For each participant included in the study, a QALY score over the 4-week period was estimated using the area under the curve approach.[29] Total healthcare costs over the 4-week period were calculated by multiplying the resource items used by the respective unit cost and summing over all items. Missing costs and health outcomes were imputed using a multiple imputation methodology. The technique used was predictive mean matching and the imputation model included 25 imputed datasets [30]

Multilevel modelling, recommended for the economic evaluation of cluster and multinational trials, was used for data analysis.[31-32] Dependent variables included total cost, QALYs and antibiotic prescribing. The model controlled for day 1 EQ-5D, gender, age, smoking, sex, crepitations, wheeze, pulse rate higher than 100 beats per minute, temperature higher than 37.8 degrees Celsius, respiratory rate, blood pressure and duration of cough. These variables were controlled for in order to adopt a similar approach to the clinical study. To explore country variation in the cost-effectiveness of the interventions, adjusted country-specific cost-effectiveness estimates were also obtained using a Bayesian approach.[33] Minimally informative prior distributions were placed on all model parameters.[34] All analysis was carried out in STATA 12, Winbugs 14 and R statistical software. Model estimates of the difference in costs, QALYs and antibiotic prescribing were used to derive an incremental cost-per-QALY-gained and an incremental cost-per-percentage-reduction in antibiotic prescribing.

For the CUA, we used the NICE recommended threshold of between £20,000 to £30,000 (€24,655 to €36,928) per QALY to judge the cost-effectiveness of the interventions.[35]

A 'Within the table' analysis was adopted to account for the factorial nature of the trial.[36-37] This method assumes that the interventions are not independent i.e. the costs and effects of communication skills are influenced by the inclusion of CRP testing and vice-versa. This approach, which considers each treatment option individually, was used for the base-case analysis. All interventions were ordered in terms of increasing cost, for costs, QALYs and percentage reduction in antibiotic prescribing for each treatment arm to be compared incrementally. The most cost-effective option was selected based on the principles of dominance (where an intervention is less costly and more effective than the appropriate comparator(s)) and extended (weak) dominance (where an intervention is ruled out if the Incremental cost-effectiveness ratio (ICER) is greater than that of a more effective intervention).[38] In addition, all interventions were compared to usual care individually.

Sensitivity analysis

Sensitivity analysis had two main foci. First, the results were compared against country-specific thresholds to determine whether the interventions are cost-effective. This analysis was limited to the CUA and of the five participating countries, only the UK has an explicit threshold (£20,000 (€24,655) to £30,000 (€36,928) per QALY gained.[35] There is no explicit threshold in the Netherlands, Belgium, Spain and Poland. However, a value of €20,000 per QALY gained is often used in the Netherlands,[39] €35,000 per QALY gained has been used to inform decision making in Belgium[40] and in Spain, it has been suggested that the threshold value should lie between €22000 and €25000 per QALY gained.[41] These values were therefore used to represent cost-effectiveness thresholds in the countries mentioned. No threshold value was identified in Poland.

Second, to further explore the impact of including the cost of resistance, sensitivity analysis focused on conducting the economic evaluation without accounting for the cost of antibiotic resistance. This analysis was limited to the CUA since the base case CUA included the cost of resistance.

Results

A total of 246 practices participated in the study and contributed 4264 participants across five European countries. The country contribution to sample size ranged from 318 (7.5%) in Belgium to 1419 (33.3%) in Poland (Table 1).

Resource use and costs

A breakdown of resource use items is presented in Table 2. Compared to the other interventions, visits to the GP and hospital admissions were lower in the usual care arm. Visits to the GP were highest in the CRP group, whilst visits to the nurse were highest in the communication skills group. As was expected, those in the CRP and combined intervention groups had more CRP tests performed. Approximately 59% of participants in the usual care arm had an antibiotic prescribed compared to approximately 34% in the combined intervention arm. Costs associated with resource use items are presented in Table 3. GP costs were highest in the CRP group whilst nurse costs were highest in the communication skills group. Costs associated with over-the-counter medication were highest in the usual care arm.

Outcomes

There was an improvement in health of participants over the 4-week period as shown by the EQ-5D scores. The scores at four weeks were higher than those at day 1 in all four treatment arms (Table 4). Overall, antibiotic prescribing was highest in the usual care group and lowest in the combined intervention group (Table 4).

Cost-utility analysis

The CUA results indicate that overall, communication skills is the most cost-effective intervention since it dominated all other interventions (Table 5). Compared to usual care, both communication skills and CRP were dominant whilst the combined intervention was dominated. Country-specific estimates showed that communication skills was the most cost-effective intervention in Belgium, UK and Netherlands. CRP is only cost-effective in Netherlands if the threshold is above €27,000 (£21,903) per QALY gained. CRP is cost-effective in Poland whilst usual care is cost-effective in Spain (Table 5 and Figures 1 and 2).

Cost-effectiveness analysis

With respect to the CEA (percentage reduction in antibiotic prescribing as an outcome), communication skills was associated with an ICER of €68.08 (£55.23) per percentage reduction in antibiotic prescribing when compared to usual care. The ICER for CRP compared to communication skills was €176.53 (£143.20) per percentage reduction in antibiotic prescribing and the ICER for the combined intervention compared to CRP was €338.89 (£274.90) per percentage reduction in antibiotic prescribing (Table 6). Compared to usual care, ICERs ranged from €68.08 (£55.23) per percentage reduction in antibiotic prescribing with communication skills to €126.21 (£102.38) per percentage reduction in antibiotic prescribing with the combined intervention. Country-specific estimates show that CRP is the most cost-effective intervention in Belgium. In the Netherlands, CRP is cost-effective if society is willing to pay around €72 (£58) per percentage reduction in antibiotic prescribing. On the other hand, communication skills is the most cost-effective in Poland, Spain and the UK (Table 6 and Figures S1 and S2).

Sensitivity analysis

In terms of comparing the results to country-specific cost-effectiveness thresholds, communication skills was cost-effective in Belgium, Netherlands and UK, CRP was cost-effective in Poland and Usual care was cost-effective in Spain (Table S1).

The results of the sensitivity analysis which excludes the cost of antibiotic resistance are presented in Table S2, Figure S3 and Figure S4, and they show that, overall, usual care is cost-effective if the cost of antibiotic resistance is not accounted for. The country-specific estimates also show that, with the exception of Belgium where communication skills was cost-effective, usual care is the most cost-effective intervention in all other countries when the cost of antibiotic resistance is not included.

Discussion

Summary of main findings

This study evaluated the cost-effectiveness of (i) training GPs in the use of CRP testing, (ii) training GPs in communication skills and (iii) training GPs in *both* CRP testing compared to usual care. In terms of cost-per-percentage reduction in antibiotic prescribing, overall, communication skills was the most cost-effective. Similarly, the CUA also showed that communication skills was the most cost-effective intervention. However, the country-specific estimates were not consistent across the CUA and the CEA. The only country where communication skills was cost-effective across both the CUA and CEA was the UK. Compared to usual care, both communication skills and CRP are cost-effective. Sensitivity analysis where the cost of resistance was not included in the CUA led to a scenario where usual care was the most cost-effective intervention overall.

Strengths and limitations of the study

There are several strengths to this study. First, the factorial nature of the study enabled the relative cost-effectiveness of four different interventions to be explored within the same trial. Second, this study utilized data from five different European countries and so the findings may be more generalisable than those obtained from previous studies conducted in single country settings. Third, the study presented country-specific cost-effectiveness estimates, and, fourth, this study explored the implications of accounting for antibiotic resistance in economic evaluations.

There are also a number of limitations. First, this study is conducted alongside a multinational, cluster randomised, factorial controlled trial, which presents additional complexities with respect to the analysis of the data. The factorial nature has the effect of reducing the sample size for any of the interventions on its own and therefore increasing the degree of uncertainty in the economic data. In this study, randomisation took place at the cluster/practice level whilst health economics outcomes such as QALYs were measured at the level of the individual. However, this has been addressed using methods that account for the hierarchical nature of the data. Second, assumptions were required to estimate country-specific unit costs where these were not available. Third, with respect to the CUA, since there is no European wide cost-effectiveness threshold, this study relied on the UK threshold to judge the cost-effectiveness of interventions. Other studies have also noted problems with regards to the choice of cost-effectiveness threshold in a multinational setting.[42] Cost-effectiveness thresholds used in the Netherlands and Spain are €20,000 and €24,000 per QALY gained respectively. Fourth, with respect to the CEA, there is no commonly accepted threshold at which achieving an amount of antibiotic prescribing would be considered cost-effective. It is therefore difficult to reach a conclusion about the cost-effectiveness of the interventions based on an accepted threshold for the analysis. This study did not assess the long-term cost-effectiveness of the interventions under consideration. As a result of this, any long-term issues such as change in practice over time was not assessed. Finally, the use of estimates of the costs of antibiotic resistance is problematic given the difficulty of making such estimates.

Comparison with other studies

Other studies have reached similar conclusions about the cost-effectiveness of communication skills[20] and CRP.[20,43] This study therefore adds to the evidence about the potential benefits of CRP and communication skills, but for the first time in a rigorous experimental multinational context where the interventions have been assessed across a number of European countries. One previous study also concluded that ignoring the cost of antibiotic resistance in economic evaluations could lead to misleading conclusions,[25] a result which is similar to what was found in this study.

Policy implications and implications for future research

The results of this study indicate that communication skills is cost-effective in terms of reducing antibiotic prescribing, and the intervention may offer a cost-effective way of preserving the effectiveness of the available antibiotics in an era where pharmaceutical companies are not successfully channelling enough resources into their development.[2] Training GPs in advanced, relevant communication skills might also help to preserve the effectiveness of new antibiotics if and when they become available. Prescribing antibiotics to patients who are likely to benefit is one of the aims of the UK government's five-year strategy on antibiotics[44] and the widespread use of advanced, specific communication skills is likely to help achieve this aim since the intervention is both effective and cost-effective in terms of reducing antibiotic prescribing.

Compared to usual care, CRP was also found to be cost-effective. Thus, CRP represents a more cost-effective means of reducing unnecessary antibiotic prescribing compared to usual care. However, this was not as cost-effective as communication skills. The National Institute for Health and Care Excellence (NICE) in the UK and Nederlands Huisartsen Genootschap (NHG) in the Netherlands have recommended that point of care CRP testing should be considered for patients presenting with symptoms of LRTI if it is not clear whether antibiotics should be prescribed.[45-46] Similarly, Belgium has implemented training in communication skills at the national level. However, if governments and policy makers choose to adopt these interventions, the current cost of implementing them on a large scale needs to be considered. The other issue that needs to be considered is whether the widespread use of testing will 'medicalise' largely self-limiting illnesses – by creating the perception that consulting for a test is necessary to decide whether treatment is necessary - and thus increase consultations, potentially reducing efficiency and limiting the ability to reduce antibiotic prescribing.[47]

The interventions considered in this study (communication skills and CRP) are primarily aimed at reducing the prescription of antibiotics by GPs and a potential question is whether the QALY, which is focused primarily on measuring health gain, should be the main outcome measure for interventions of this type. Whilst withholding antibiotics may lead to a reduction in health in the short-run,[20] this may be considered acceptable in the context of prescribing antibiotics for future use, with the subsequent future health gain for the individual and society that implies. It is therefore suggested that the impact of antibiotic resistance should be accounted for in all economic evaluations of interventions that consider antibiotic use. Our study attempted to account for this by including a cost of resistance in the analysis and this clearly had a significant impact on the results that we obtained. The implication of not accounting for resistance is that policy makers may be led to believe that such an intervention may not provide value for money and not implement interventions that do not appear cost-effective because the resistance costs are excluded. However, there are clear benefits to society when antibiotic prescribing is reduced. This study recommends that future research should focus on how to capture and include the cost of resistance in economic evaluations.

In conclusion, internet-based training in communication skills is a cost-effective intervention to reduce antibiotic prescribing for respiratory tract infections in primary care if the cost of antibiotic resistance is accounted for.

Funding

European Commission Framework Programme 6, National Institute for Health Research, Research Foundation Flanders.

Transparency declarations

None to declare.

References

1. Plowman R, Graves N, Griffin M, *et al*. 1999 The socio-economic burden of hospital acquired infection Public Health Laboratory Service http://webarchive.nationalarchives.gov.uk/20120510093318/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4089725.pdf
2. O'Neill J 2014 Antimicrobial resistance: Tackling a crisis for the health and wealth of nations: Review on antimicrobial resistance tackling drug-resistance globally http://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf
3. Simpson SA, Wood F, Butler CC General Practitioners' perceptions of antimicrobial resistance: a qualitative study *J Antimicrob Chemother* 2007; **59**: 292-296
4. Yardley L, Douglas E, Anthierens S *et al*. Evaluation of a web-based intervention to reduce antibiotic prescribing for LRTI in six European countries: quantitative process analysis of the GRACE/INTRO randomised controlled trial *Implement Sci* 2013; **8**:134
5. Coenen S, Francis N, Kelly M *et al*. (2013) Are patients views about antibiotics related to clinician perceptions, management and outcome? A multi-country study in outpatients with acute cough *PLOS ONE* 2013; **8**: e76691

6. Little P, Stuart B, Smith S *et al*. Antibiotic prescribing strategies and adverse outcome for uncomplicated lower respiratory tract infections: prospective cough complication cohort (3C) study *BMJ* 2017;**357**:j2148
7. Little P, Rumsby K, Kelly J *et al*. Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection. *JAMA J AM MED ASSOC* 2005; **293**:3029-35.
8. Carlet J, Collignon P, Goldman D *et al*. Society's failure to protect a precious resource: antibiotics. *Lancet* 2011; **378**: 369-71
9. Piddock L The crisis of no new antibiotics – what is the way forward? *Lancet Infect Dis* 2012; **12**: 249-253
10. Smith RD and Coast J The true cost of antimicrobial resistance *BMJ* 2013; **346**:f1493
11. World Health Organisation (2017) Antimicrobial agents in clinical development: An analysis of the antimicrobial clinical development including tuberculosis http://apps.who.int/iris/bitstream/10665/258965/1/WHO-EMP-IAU-2017.11-eng.pdf?ua=1
12. Martens JD, Winkens RAG, van der Weijden T Does a joint development and dissemination of multidisciplinary guidelines improve prescribing behaviour: a pre/post study with concurrent control group and a randomised trial. *BMC Health Serv Res* 2006; **6**:145
13. Van Driel ML, Coenen S, Dirven K *et al*. What is the role of quality circles in strategies to optimise antibiotic prescribing? A pragmatic cluster-randomised controlled trial in primary care. *Qual Saf Health Care* 2007;**16**: 197-202
14. Simpson SA, Butler CC, Hood K *et al*. Stemming the tide of antibiotic resistance (STAR): a protocol for a trial of a complex intervention addressing the 'why' and

'how' of appropriate antibiotic prescribing in general practice *BMC Fam Pract* 2009; **10**:20

15. Cals JW, Butler CC, Hopstaken RM *et al*. Effect of point of care testing for C reactive and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. *BMJ* 2009; **338**:b1374
16. Butler CC, Simpson SA, Dunstan F *et al*. Effect of a multifaceted educational programme to reduce antibiotic dispensing in primary care: practice based randomised controlled trial *BMJ* 2012; **344**: d8173
17. Anthierens S, Tonkin-Crine S, Cals JW *et al*. Clinicians' views and experiences of interventions to enhance the quality of antibiotic prescribing for acute respiratory tract infections *J Gen Intern Med* 2014; **30**:408-16
18. Anthierens S, Tonkin-Crine S, Douglas E *et al*. General practitioner' views on the acceptability and applicability of a web-based intervention to reduce antibiotic prescribing for acute cough in multiple European countries: a qualitative study prior to a randomised trial *BMC Fam Pract* 2012; **13**: 101
19. Little P, Stuart B, Francis N *et al*. Effect of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial controlled trial *Lancet* 2013; **382**: 1175-1182
20. Cals JW, Ament AJ, Hood K *et al*. C-reactive protein point of care testing and physician communication skills training for lower respiratory tract infections in general practice: economic evaluation of a cluster randomized trial. *J Eval Clin Pract* 2011; **17**:1059-69.
21. Oppong R, Coast J, Hood K *et al*. Resource use and costs of treating acute cough/lower respiratory tract infections in 13 European countries: results and challenges. *Eur J Health Econ* 2011;**12**:319-29

22. World Bank. The World Bank Consumer Price Index. 2016. https://data.worldbank.org/indicator/FP.CPI.TOTL?locations=US
23. Schulman K, Burke J, Drummond M *et al*. Resource costing for multinational neurologic clinical trials: methods and results. *Health Econ* 1998;**7**:629-38.
24. Coast J, Smith RD, Millar MR. Superbugs: should antimicrobial resistance be included as a cost in economic evaluation? *Health Econ* 1996; **5**: 217-26.
25. Oppong, R., Smith, R. D., Little, P *et al.* Cost effectiveness of amoxicillin for lower respiratory tract infections in primary care: an economic evaluation accounting for the cost of antimicrobial resistance. *Brit J Gen Pract* 2016; **66**, e633-e639.
26. Rabin R, de Charro F EQ-5D: a measure of health status from the EuroQol Group *Ann Med* 2001; **33**: 337-43
27. Greiner W, Weijnen T, Nieuwenhuizen M *et al*. A single European currency for EQ-5D health states. *Eur J Health Econ* 2003;**4**:222-31.
28. Oppong R, Kaambwa B, Nuttall J *et al*. Assessment of the Construct Validity of EQ-5D in patients with acute cough/LRTI *Appl Res Qual Life* 2011; **6**: 411-423
29. Matthews, J., Altman, D. G., Campbell, M *et al*. Analysis of serial measurements in medical research. *BMJ*, 1990; **300**: 230-235.
30. Rubin DB. Multiple imputation for nonresponse in surveys. New York, USA: John Willey & Sons 1987.
31. Gomes, M. Ng ES, Grieve R *et al*. Developing appropriate methods for cost-effectiveness analysis of cluster randomised trials *Med Decis Making* 2012; **32**: 350-61
32. Manca, A., Sculpher, M.J., Goeree, R. The analysis of multinational cost-effectiveness data for reimbursement decisions: a critical appraisal of recent methodological developments. *PharmacoEconomics*, 2010; **28**: 1079-1096

33. Manca A, Lambert PC, Sculpher M *et al*. Cost-effectiveness analysis using data from multinational trials: The use of bivariate hierarchical modelling *Med Decis Making* 2007; **27:** 471-490

34. Lambert PC, Sutton AJ, Burton PR, et al. How vague is vague? A simulation study of the impact of the use of vague prior distributions in MCMC using Win BUGS. *Stat Med 2005;* ***24****: 2401-2428*

35. Appleby, J., Devlin, N., & Parkin, D. 2007. NICE's cost effectiveness threshold. *BMJ*, **335**, 358

36. Dakin, H, Gray A (2017) Economic evaluation of factorial randomised controlled trials: challenges, methods and recommendations *Stat Med* 2017; **36**: 2814-2830

37. Frempong S, Goranitis I, Oppong R. Economic evaluation alongside factorial trials: A systematic review of the literature Exp Rev Pharmacoeconomics Out Res 2015; **15**: 801-11

38. Cantor SB. Cost-Effectiveness Analysis, Extended Dominance, and Ethics A Quantitative Assessment. *Med Decis Making.* 1994;**14**:259-265.

39. Boersma C, Broere A, Postma MJ Quantification of the potential impact of cost-effectiveness thresholds on Dutch drug expenditures using retrospective analysis *Value Health* 2010;**13**:853-856

40. Jit M, Bilcke J, Mangen MJ *et al*. The cost-effectiveness of rotavirus vaccination. A comparative analysis for five European countries and transferability in Europe. *Vaccine* 2009; **27**: 6121-6128

41. Vallejo-Torres L, Garcia-Lorenzo B, Serrano-Aguilar P Estimating a cost-effectiveness threshold for the Spanish NHS. *Health Econ.* 2018; **27:** 746-761

42. Mittmann, N., Au, H.J., Tu, D *et al*. Prospective cost-effectiveness analysis of cetuximab in metastatic colorectal cancer: evaluation of National Cancer Institute of Canada Clinical Trials Group CO. 17 trial. *J Natl Cancer Inst*, 2009; **101**: 1182-1192

43. Oppong R, Jit M, Smith RD *et al*. Cost-Effectiveness of Point of Care CRP Testing to Inform Antibiotic Prescribing Decisions *Brit J Gen Pract* 2013; **63**: e465- e471

44. Department of Health UK Five Year Antimicrobial Resistance Strategy 2013 to 2018 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf

45. National Institute for Health and Care Excellence (2014) Pneumonia Diagnosis and management of community and hospital-acquired pneumonia in adults. NICE clinical guideline 191 https://www.nice.org.uk/guidance/cg191/resources/guidance-pneumonia-pdf

46. Netherlands huisartsen genootschap (2013) Acute Cough M78 https://guidelines.nhg.org/wp-content/uploads/2014/05/summary-card-m78-acute-cough.pdf

47. HardyV, Thompson M, Keppel GA, *et al*. Qualitative study of primary care clinicians' views on point of care testing for C-reactive protein for acute respirator tract infections in family medicine *BMJ Open* 2017;**7**:e0120503

TABLE 1: Source of valuation data and country contribution to sample size

	Belgium	Netherlands	Poland	Spain	UK
GP Visits	1	1	1	1	2
Nurse Visits	N/A	1	1	1	2
Out of hours GP	9	9	9	9	2
Walk in centre	N/A	1	1	1	1
Hospital Admissions	1	1	1	1	8
Investigations	9	9	9	9	8
Medication	6	5	1,9	3,1	4
Contribution to sample size	318 (7.5%)	329 (7.7%)	1419 (33.3%)	1318 (30.9%)	880 (20.6%)

1= Previous study, 2= Curtis L (www.pssru.ac.uk), 3= www.vademecum.es, 4= British National Formulary (www.bnf.org), 5= Dutch healthcare insurance board (www.medicijnkosten.nl), 6= www.bcfi.be, 7= www.http://riziv.fgov.be, 8= NHS Reference costs 9= Market basket approach

TABLE 2: Mean (SD) Resource use for complete case analysis

	Usual care (n=515)	CRP no Comm (n=660)	Comm no CRP (n=740)	CRP comm (n=709)
		PRIMARY CARE VISITS [Mean (SD)]		
GP visits	0.194 (0.472)	0.355 (0.762)	0.284 (0.713)	0.236 (0.596)
Nurse Visits	0.016 (0.206)	0.045 (0.323)	0.103 (0.741)	0.039 (0.263)
Out hours GP visits	0.015 (0.271)	0.006 (0.095)	0.023 (0.182)	0.016 (0.163)
		SECONDARY CARE VISTIS [Mean (SD)]		
Hospital emergency visits	0.002 (0.044)	0.003 (0.054)	0.018 (0.134)	0.016 (0.155)
Walk in centre visits	0.004 (0.087)	0.002(0.039)	0.022 (0.186)	0.035 (0.383)
Specialist visits	0.004 (0.062)	0.018 (0.155)	0.028 (0.222)	0.023 (0.218)
Admissions	0.010 (0.182)	0.026 (0.379)	0.019 (0.320)	0.030 (0.394)
		PRESCRIPTIONS n (%)		
Antibiotic prescription	307 (59.61%)	222 (33.64%)	303 (40.95%)	242 (34.13%)
Over the counter medication	346 (67.18%)	419 (63.48%)	451 (60.95%)	441 (62.20%)
CRP test	12 (2.33%)	441 (66.82%)	57 (7.70%)	461 (65.02%)

TABLE 3: Costs (Complete case analysis) (€)

	Usual care (n=515)	CRP no Comm (n=660)	Comm no CRP (n=740)	CRP comm (n=709)
		PRIMARY CARE VISITS		
GP visits	€3.44 (10.27)	€4.68 (11.23)	€4.60 (13.90)	€3.65 (10.12)
Nurse Visits	€0.22 (3.12)	€0.32 (3.01)	€1.36 (9.95)	€0.49 (4.71)
Out hours GP visits	€5.30 (92.83)	€2.04 (32.27)	€8.07 (63.65)	€5.36 (56.01)
		SECONDARY CARE VISTIS		
Hospital emergency visits	€0.27 (6.22)	€0.41 (7.48)	€2.60 (18.73)	€2.16 (21.30)
Walk in centre visits	€0.09 (2.03)	€0.03 (0.90)	€0.52 (4.52)	€0.78 (7.90)
Specialist visits	€0.84 (13.54)	€3.75 (31.70)	€5.58 (44.60)	€4.83 (46.70)
Admissions	€4.78 (89.56)	€12.20 (179.20)	€9.08 (150.58)	€13.92 (186.81)
		OTHER COSTS		
Prescription	€11.96 (26.87)	€8.74 (19.32)	€9.79 (19.04)	€11.99 (34.64)
OTC medication	€6.55 (17.36)	€4.48 (12.95)	€4.52 (12.65)	€6.18 (17.32)
CRP test	€0.19 (1.23)	€5.24 (3.74)	€0.28 (1.07)	€4.88 (3.79)
Trial intervention cost[a]	€0	€11.42 (7.45)	€5.62 (3.69)	€13.43 (8.53)
Resistance cost	€105.39 (94.01)	€57.29 (84.86)	€66.09 (84.49)	€60.34 (88.02)

[a] Cost associated with delivering the trial interventions

TABLE 4: Mean EQ-5D scores over 4 weeks and antibiotic prescribing (Complete cases)

	Usual care (n=515)	CRP no Comm (n=660)	Comm no CRP (n=740)	CRP comm (n=709)
		EQ-5D		
Day 1	0.717 (0.216)	0.729 (0.212)	0.693 (0.228)	0.710 (0.223)
Week 1	0.816 (0.197)	0.817 (0.207)	0.786 (0.214)	0.792 (0.210)
Week 2	0.884 (0.176)	0.881 (0.182)	0.864 (0.185)	0.869 (0.186)
Week 3	0.898 (0.170)	0.899 (0.176)	0.894 (0.176)	0.893 (0.174)
Week 4	0.906 (0.165)	0.907 (0.169)	0.903 (0.168)	0.899 (0.169)
		Antibiotic prescribing		
Antibiotic Prescribing	0.596 (0.491)	0.336 (0.473)	0.409 (0.492)	0.341 (0.474)

TABLE 5: Overall and country-specific cost-effectiveness (Cost-utility analysis)

	Cost[a]	QALY	ICER	ICER (compared to UC)
Overall (n=4264)				
CRP&Comm	94.36	0.0648	Dominated by Comm	Dominated by UC
Usual care	92.46	0.065	Dominated by Comm	N/A[f]
CRP	87.41	0.0651	Dominated by Comm	Dominates UC
Comm	83.21	0.0651	N/A[f]	Dominates UC
Belgium (n=318)				
Comm	93.28	0.0651	3450[e]	7120[b]
CRP&comm	92.59	0.0649	7343[c]	8038[b]
CRP	87.45	0.0642	12900[b]	12900[b]
Usual care	86.16	0.0641	N/A[f]	N/A[f]
Netherlands (n=329)				
CRP&Comm	84.99	0.0649	Dominated by CRP	Dominated by UC
Usual care	75.52	0.065	Dominated by CRP	N/A[f]
CRP	73.41	0.0656	27,186[c]	Dominates UC
Comm	54.38	0.0649	N/A[f]	N/A
Poland (n=1419)				
Usual care	143.41	0.0663	49129[c]	N/A[f]
Comm	114.37	0.0656	Dominated by CRP	41486[g]
CRP&Comm	110.95	0.0652	Dominated by CRP	29509[g]
CRP	109.02	0.0656	N/A[f]	49129[g]
Spain (n=1318)				
CRP&Comm	78.71	0.0648	Dominated by Usual care	Dominated by UC
CRP	70.86	0.0656	Dominated by Usual care	Dominated by UC
Usual care	66.46	0.0659	1000[d]	N/A[f]
Comm	65.86	0.0653	N/A[f]	1000[g]
UK (n=880)				
CRP&Comm	106.57	0.0641	Dominated by Comm	25050[b]
Usual care	101.56	0.0639	Dominated by Comm	N/A[f]
CRP	98.75	0.0645	Dominated by Comm	Dominates UC
Comm	98.05	0.0648	N/A[f]	Dominates UC

[a] Costs includes the costs associated with antibiotic resistance [b] Compared to usual care [c] Compared to CRP training [d] Compared to communication skills training [e] Compared to training in both CRP testing and communication skills [f] not applicable, this is the reference case [g] ICER value represents a comparison of usual care versus the respective intervention since the ICER generated from a comparison of the respective intervention with usual care represents a willingness to accept a loss in benefit, rather than a willingness to pay for a gain in benefit. UC=usual care

TABLE 6: Overall and country-specific cost-effectiveness (Cost-effectiveness analysis)

	Cost[a]	**Outcome**	**ICER**	**ICER (compared to UC)**
		Overall (n=4264)		
CRP + Comm	60.32	0.8003	338.8889[b]	126.209[b]
CRP	49.34	0.7679	176.5343[d]	95.44643[b]
Comm	39.56	0.7125	68.8019[b]	68.8019[b]
Usual care	27.96	0.5439	N/A[f]	N/A[f]
		Belgium (n=318)		
CRP + Comm	62	0.8216	323.4528[b]	234.3308[b]
CRP	52.07	0.7909	26.85393[d]	203.7946[b]
Comm	49.68	0.7019	26350[b]	26350[b]
Usual care	33.81	0.7013	N/A[f]	N/A[f]
		Netherlands (n=329)		
CRP + Comm	58.47	0.8409	1929.73[c]	126.6091[b]
CRP	44.19	0.8335	72.67583[b]	72.67583[b]
Usual care	26.21	0.5861	Dominated by Comm	N/A[f]
Comm	26	0.7894	N/A[f]	Dominates UC
		Poland (n=1419)		
CRP + Comm	61.3	0.7366	189.8754[c]	81.94658[b]
CRP	49.11	0.6724	92.14953[d]	55.44933[b]
Comm	44.18	0.6189	46.00962[b]	46.00962[b]
Usual care	34.61	0.4109	N/A[f]	N/A[f]
		Spain (n=1318)		
CRP + Comm	47.5	0.8044	Dominated by CRP	162.4065[b]
CRP	39.53	0.8156	145.0094[d]	100.5685[b]
Comm	31.83	0.7625	78.13688[b]	78.13688[b]
Usual care	23.61	0.6573	N/A[f]	N/A[f]
		UK (n=880)		
CRP + Comm	74.46	0.8066	202.439[c]	112.511[b]
CRP	59.52	0.7328	170.1754[d]	95.16466[b]
Comm	49.82	0.6758	82.03317[b]	82.03317[b]
Usual care	23.11	0.3502	N/A[f]	N/A[f]

[a] Costs excludes the costs associated with antibiotic resistance [b] Compared to usual care [c] Compared to CRP training [d] Compared to communication skills training [e] Compared to training in both CRP testing and communication skills [f] not applicable, this is the reference case UC=usual care

Figure 1: Cost-effectiveness plane (cost-utility analysis)

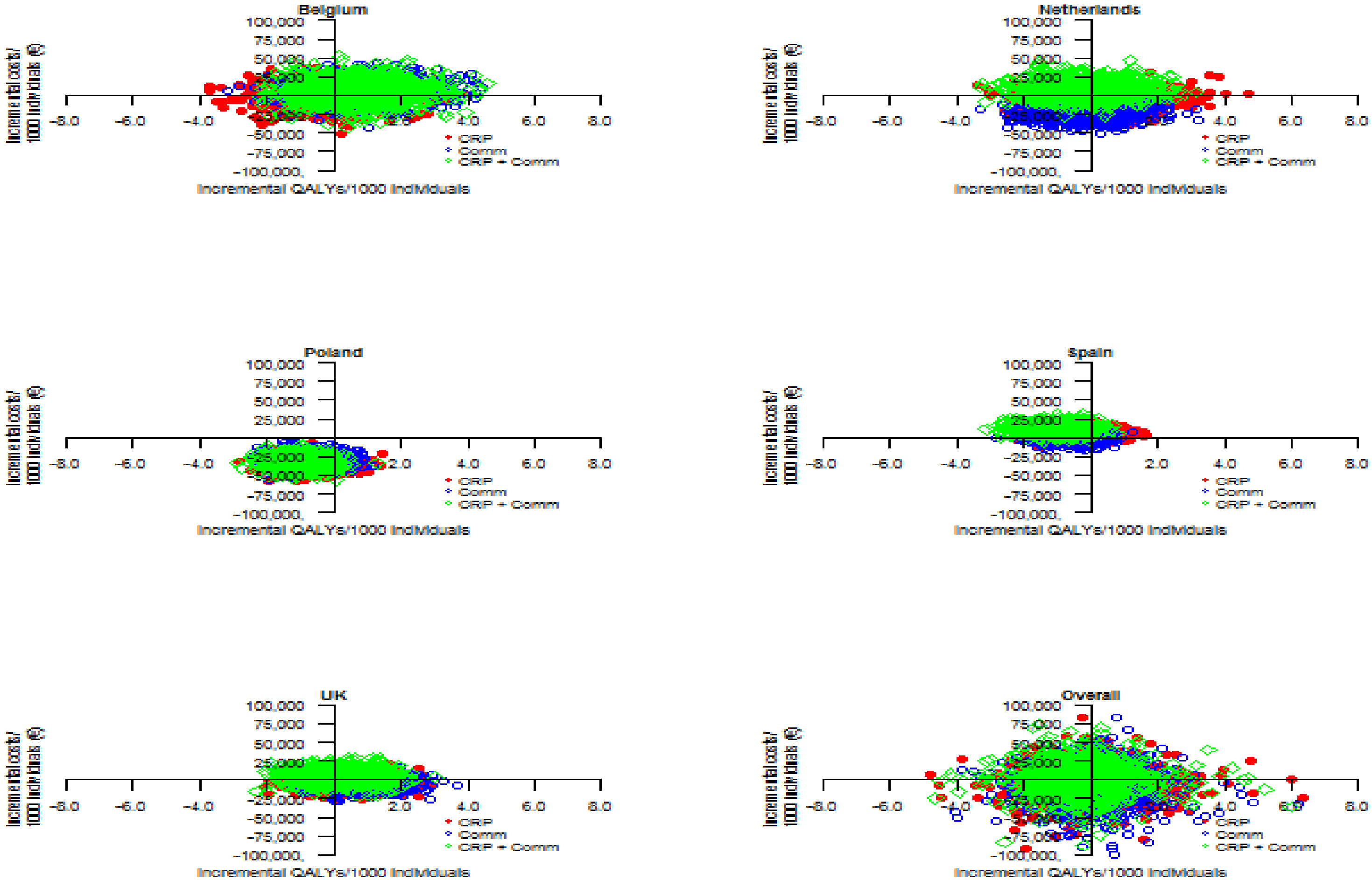

Figure 2: Cost-effectiveness acceptability frontier (cost-utility analysis)